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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

AKIHIRO KISHISHITA ET AL

: GROUP ART UNIT: 1621

SERIAL NO: 09/708,006

FILED: NOVEMBER 8, 2000

: EXAMINER: ZUCKER

FOR: NOVEL ASPARTAME
DERIVATIVE CRYSTAL AND
PROCESS FOR PRODUCING
THE SAME

COPY

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DECLARATION UNDER 37 C.F.R. §1.132

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Now comes TATSUKI KASHIWAGI, who deposes and states that:

1. That I am a graduate of University of Tokyo and received my bachelor's degree in the year 1989 and Ph.D. in the year 1999.

2. That I have been employed by Ajinomoto Company Inc. for twelve years as a research scientist in the fields of the X-ray crystallography and X-ray powder diffraction ("XRPD").

3. Solid materials can be in the crystalline state or in the amorphous state. Solid materials in the crystalline state are composed of numerous fine crystals. In a single crystal, molecules or ions comprising the material are regularly and iteratively arranged. The minimum unit of the three-dimensional iteration in the crystal is called a "unit cell" and is defined as the basic parallelepiped shaped block from which the whole volume of the crystal may be built by regular assembly of these block. As shown in Figure 1 (see below), the axial lengths of the

unit cell and the angles between these axes (cell parameters) are, by convention, defined as a , b , c , α , β , and γ , respectively.

4. Even in the same material, several kinds of crystalline states (crystal forms) can exist. This phenomenon is designated as “polymorphism.” Among organic compounds, crystals which are composed of the same molecule with different amounts of crystallizing solvents like waters are often observed. The term “pseudo-polymorphism” is often used for such situation. Between the different crystal forms related by the polymorphism or pseudo-polymorphism, the molecular arrangements and interactions in the crystals are drastically different from each other.

5. As a result, polymorph or pseudo-polymorph related crystal forms possess a lot of differing characteristics, including cell parameters, crystalline morphology, solubility, melting point, density, and so on. The differences in these characteristics, especially the crystalline morphology and the solubility, largely influence the industrial processing of the crystalline materials. Therefore, even if one crystal form has already been known, the discovery of another new crystal form which has more favorable physicochemical properties should be regarded as a new invention.

6. For over a half century, XRPD has been used to identify and characterize crystalline powders. In order to discriminate between crystalline powder samples which commonly contain the same material but belong to the different crystal forms, XRPD is the most powerful and convenient method. The main reason why XRPD can be applied to the discrimination of polymorph or pseudo-polymorph crystalline powders is that each crystal form possesses its own unique cell parameters. For example, it is known that glutamic acid has two different crystal forms, that is, an α -form (Hirayama et al., Bull. Chem. Soc. Jpn., vol. 53, p. 30 (1980)) and a β -form (Hirokawa, Acta Cryst., vol. 8, p. 637 (1955)). Their cell parameters are as follows:

α -form : $a = 7.068\text{\AA}$, $b = 10.277\text{\AA}$, $c = 10.277\text{\AA}$, $\alpha = \beta = \gamma = 90^\circ$,

β -form : $a = 5.17\text{\AA}$, $b = 17.34\text{\AA}$, $c = 6.95\text{\AA}$, $\alpha = \beta = \gamma = 90^\circ$,

demonstrating that the values of a , b , and c are completely different between the two crystal forms.

7. If a crystalline sample is irradiated with a monochromatic X-ray beam, a lot of diffracted X-rays emerge at the particular angles against the incident X-ray beam (diffraction angles). The conditions for a diffracted X-ray are given by the following relation

$$n\lambda = 2d \sin \theta,$$

where, n is an integer, λ is the wavelength of the X-ray, d is the interplanar spacing between successive atomic planes in the crystal, and θ is the angle between the atomic plane and both the incident and diffracted beam. This fundamental relation is known as the Bragg equation or Bragg's law and is schematized in Figure 2 (see below). As shown in Figure 2, the diffraction angle can be considered as 2θ .

8. In the measurement of XRPD, the wavelength of the X-ray is usually fixed to a particular value, most commonly, to 1.5418\AA (the characteristic X-ray of Cu K α). Therefore, the diffraction angle 2θ can be regarded as a function of d . The interplanar spacing d is represented by the following relation:

$$1/d = (h^2 a^{*2} + k^2 b^{*2} + l^2 c^{*2} + 2klb^*c^* \cos \alpha^* + 2lhc^*a^* \cos \beta^* + 2hka^*b^* \cos \gamma^*)^{1/2},$$

where, h , k , and l are integers, and a^* , b^* , c^* , α^* , β^* , and γ^* are the parameters which are closely related to the cell parameters by the following equations

$$a^* = bc \sin \alpha / V$$

$$b^* = ca \sin \beta / V$$

$$c^* = ab \sin \gamma / V$$

$$\cos \alpha^* = (\cos \beta \cos \gamma - \cos \alpha) / \sin \beta \sin \gamma$$

$$\cos \beta^* = (\cos \gamma \cos \alpha - \cos \beta) / \sin \gamma \sin \alpha$$

$$\cos \gamma^* = (\cos \alpha \cos \beta - \cos \gamma) / \sin \alpha \sin \beta,$$

where, V is the volume of the unit cell. Thus, the diffracted X-rays of a crystalline powder occurs only at the particular 2θ angles which are determined by its cell parameters.

Resultantly, the XRPD patterns of the same materials belonging to different crystal forms demonstrate diffraction peaks with discordant 2θ angles.

9. Of course, the intensities of the diffracted X-rays are also important for identifying and characterizing crystalline powders. In the case when the effects of the apparatus, the peak overlap, and the crystalline morphology etc. are negligible, the intensities of the diffraction peaks basically depend on the molecular arrangement in the crystal, suggesting that the strength order of the diffraction peaks is basically conserved in the XRPD patterns of one crystal form.

10. It is a conventional identification method for a specific crystal to find crystal(s) having the same three strongest peaks of the specific crystal on XRPD data bases and, when found, to analyze coincidence of other peaks between them. In general cases, the crystal can be identified when the strongest eight peaks are coincident. In the case of the specific crystals of a particular compound, for instance, A-type crystals, C-type crystals, or other types crystals of neotame, it is possible to identify one of them by using one strong and characteristic peak.

11. Figure 3 (see below) demonstrates the XRPD patterns of *N*-(3,3-dimethylbutyl)-APM (Neotame). In the XRPD of the A-type crystal form which is obtained using the processes and recrystallization methods described in U.S. Patent No. 5,480,668 (Nofre et al), the intense diffraction peaks occur at the 2θ angles of 6.0° , 8.2° , 14.2° , 16.5° , 16.8° , 17.7° , 20.3° , 20.8° , 22.8° , 26.0° , 26.2° , and 26.6° . On the other hand, the intense diffraction peaks of the XRPD of the C-type crystal form obtained by the method disclosed in U.S. Patent Application Serial No. 09/708,006 occur at the 2θ angles of 6.3° , 7.1° , 15.1° , 17.3° , 17.7° ,

19.8°, 20.3°, 21.7°, 22.7°, and 26.5°. Based on the 2θ angles of the diffractions, the two XRPD patterns are clearly different from each other. The XRPD patterns of D-type and E-type crystals are also completely different from that of C-type crystals. These XRPD patterns were collected using the same apparatus (Philips, X'Pert-MPD), suggesting that the systematic error of 2θ angles is negligible and that the discordance of 2θ angles is derived from the differences of the crystals themselves. Crystals of Neotame can be identified as C-type crystals of neotame when a diffraction peak at 7.1° is observed, because this peak is characteristic of the C-type crystal form. The differences in the other diffraction peaks observed between the two types of crystals further support the conclusion that the C-type crystal form is a completely different crystal form from the A-type crystal form.

12. Furthermore, the A-type and C-type crystals contain 3-6 wt% and <3 wt% of water, respectively. These results suggest that these Neotame crystals are related by the pseudo-polymorphism relationship. However, on the other hand, the solubility of the C-type crystal is larger than that of the A-type crystal.

13. In conclusion, from the above observations, I believe that the Neotame C-type crystal form is a novel material with more favorable properties and it should be regarded as the new invention.

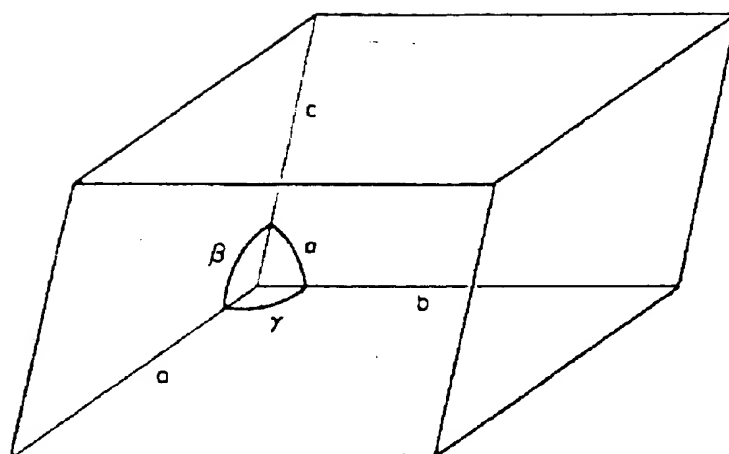


Figure 1. Unit Cell of a crystal

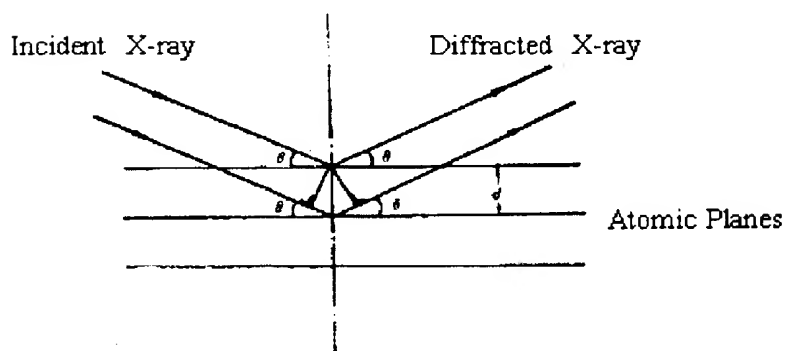


Figure 2. Bragg Equation

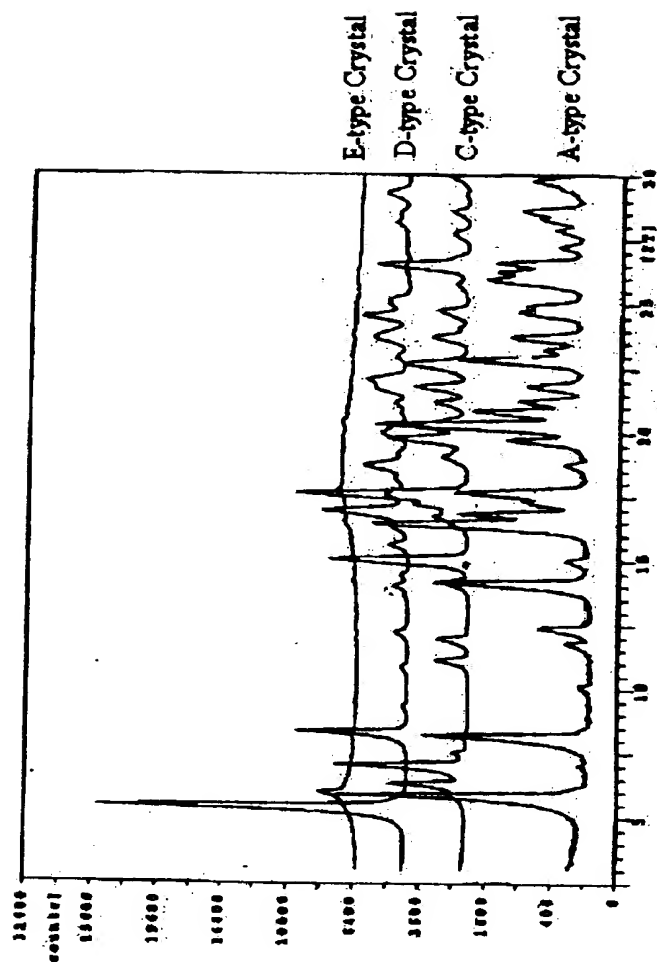


Figure 3. XRPD Patterns of Neotame Crystals

14. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

15. Further Declarant saith not.

Tatsuki Kashiwagi

TATSUKI KASHIWAGI

Date October 31, 2002